

CLAIMS

1. A liquid, aqueous composition, comprising
 - (i) a modified factor VII polypeptide;
 - 5 (ii) an agent suitable for keeping pH in the range of from about 4.0 to about 8.0;
 - (iii) an antioxidant; and
 - (iv) an agent selected from the list of: a calcium salt, a magnesium salt, or a mixture thereof.
- 10 2. A composition according to claim 1, wherein the pH is kept in the range of from about 4.0 to about 7.0.
3. A composition according to claim claim 1, wherein the antioxidant (iii) is selected from the group consisting of: L- or D-methionine, a methionine analogue, a methionine-containing pep-
15 tide, a methionine-homologue, ascorbic acid, cysteine, homocysteine, glutathione, cystine, and cyststathionine.
4. A composition according to claim 3, wherein the antioxidant is L-methionine.
- 20 5. A composition according to claim 1, wherein the antioxidant is present in a concentration of from about 0.1 to about 5.0 mg/ml.
6. A composition according to claim 1, further comprising (v) a tonicity modifying agent.
- 25 7. A composition according to claim 6, wherein the tonicity modifying agent (v) is selected from the group consisting of: a neutral salt; a mono-, di- or polysaccharide; a sugar alcohol; an amino acid; or a small peptide, and a mixture of at least two of said modifying agents.
8. A composition according to claim 7, wherein tonicity modifier is mannitol and/or a neutral
30 salt.
9. A composition according to claim 6, wherein the tonicity modifying agent (v) is present in a concentration of from 1 mM to 500 mM.
- 35 10. A composition according to claim 9, wherein the concentration is 10 – 250 mM.
11. A composition according to claim 1, further comprising (vi) a non-ionic surfactant.

12. A composition according to claim 11, wherein the non-ionic surfactant is a polysorbate or a poloxamer or a polyoxyethylene alkyl ether.
13. A composition according to claim 1, wherein the agent (ii) suitable for keeping pH in the
5 range of from about 4.0 to about 8.0 is selected from the group consisting of acids and salts of: citrate, acetate, histidine, malate, phosphate, tartaric acid, succinic acid, MES, HEPES, Imidazol, TRIS, lactate, glycylglycin, PIPES, glycine, and a mixture of at least two of said agents.
14. A composition according to claim 13, wherein the concentration of the agent (ii) is from
10 about 1 mM to about 50 mM.
15. A composition according to claim 14, wherein the concentration of the agent (ii) is about 10 mM.
16. A composition according to claim 1, wherein the calcium and/or magnesium salt (agent (iv)) is present in a concentration of from about 5 mM to about 150 mM.
17. A composition according to claim 1, wherein the calcium salt is selected from the group consisting of: calcium chloride, calcium acetate, calcium gluconate, and calcium laevulate.
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18. A composition according to claim 1, wherein the magnesium salt is selected from the group consisting of: magnesium chloride, magnesium acetate, magnesium sulphate, magnesium gluconate, and magnesium laevulate.
19. A composition according to claim 1, further comprising (vii) a preservative selected from the group consisting of phenol, benzyl alcohol, orto-cresol, meta-cresol, para-cresol, methyl paraben, propyl paraben, benzaconium chloride, and benzaethonium chloride.
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20. A composition according to claim 1, wherein said composition is isotonic.
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21. A composition according to claim 1, which is formulated for pharmaceutical administration.
22. A composition according to claim 1, wherein said modified Factor VII polypeptide is stable for at least 6 months at 2-8°C.
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23. A composition according to claim 1, wherein the modified factor VII polypeptide has a biological activity relative to wild-type factor VIIa of less than about 25% of the specific activity of

wild-type factor VIIa when tested in one or more of a clotting assay, proteolysis assay, or TF binding assay.

24. A composition according to claim 1, wherein the modified factor VII polypeptide is selected from the group consisting of: human and bovine factor VII, wherein the active site residue Ser344 is modified, replaced with Gly, Met, Thr, or Ala; human factor VII, wherein the residue Lys341 is replaced; human factor VII, wherein the residue Asp242 is replaced; human factor VII, wherein the residue His193 is replaced; FVII-(K341A); FVII-(S344A); FVII-(D242A); FVII-(H193A); a factor VII polypeptide modified in the active site by reaction with a reagent selected from the list of: peptide chloromethylketones or peptidyl chloromethanes; azapeptides; acylating agents such as various guanidinobenzoate derivatives and 3-alkoxy-4-chloroisocoumarins; sulphonyl fluorides such as phenylmethylsulphonylfluoride (PMSF); diisopropylfluorophosphate (DFP); tosylpropylchloromethyl ketone (TPCK); tosylsilylchloromethyl ketone (TLCK); nitrophenylsulphonates; heterocyclic protease inhibitors such as isocoumarines, and coumarins; a factor VII polypeptide modified in the active site by reaction with a reagent selected from the list of: L-Phe-Phe-Arg chloromethyl ketone, D-Phe-Phe-Arg chloromethyl ketone, L-Phe-Pro-Arg chloromethyl ketone, D-Phe-Pro-Arg chloromethyl ketone, L-Glu-Gly-Arg chloromethyl ketone, D-Glu-Gly-Arg chloromethyl ketone, Dansyl-L-Phe-Phe-Arg chloromethyl ketone, Dansyl-D-Phe-Phe-Arg chloromethyl ketone, Dansyl-L-Phe-Pro-Arg chloromethyl ketone, Dansyl-D-Phe-Pro-Arg chloromethyl ketone, Dansyl-L-Glu-Gly-Arg chloromethylketone, and Dansyl-D-Glu-Gly-Arg chloromethylketone.

25. A composition according to claim 24, wherein the modified factor VII polypeptide is selected from the group consisting of: FVII-(S344A); FVII-(H193A); and a factor VII polypeptide modified in the active site by reaction with a reagent selected from the group consisting of: L-Phe-Phe-Arg chloromethyl ketone, D-Phe-Phe-Arg chloromethyl ketone, L-Phe-Pro-Arg chloromethyl ketone, D-Phe-Pro-Arg chloromethyl ketone, L-Glu-Gly-Arg chloromethyl ketone, D-Glu-Gly-Arg chloromethyl ketone, Dansyl-L-Phe-Phe-Arg chloromethyl ketone, Dansyl-D-Phe-Phe-Arg chloromethyl ketone, Dansyl-L-Phe-Pro-Arg chloromethyl ketone, Dansyl-D-Phe-Pro-Arg chloromethyl ketone, Dansyl-L-Glu-Gly-Arg chloromethylketone, and Dansyl-D-Glu-Gly-Arg chloromethylketone. chloromethylketone, Dansyl-D-Phe-Pro-Arg chloromethylketone, Dansyl-L-Glu-Gly-Arg chloromethylketone, and Dansyl-D-Glu-Gly-Arg chloromethylketone.

26. A composition according to claim 1, wherein the modified factor VII polypeptide is present in a concentration of from about 0.1 mg/ml to about 15 mg/ml.

27. A method for preparing a liquid aqueous composition of a modified factor VII polypeptide, comprising providing a modified factor VII polypeptide in a solution comprising (ii) an agent suitable for keeping pH in the range of from about 4.0 to about 8.0; (iii) an antioxidant; and (iv) an agent selected from the list of: a calcium salt, a magnesium salt, or a mixture thereof.

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28. A method for inhibiting blood clotting in a subject, the method comprising administering to a subject in need thereof an effective amount of an aqueous liquid composition comprising (i) a modified factor VII polypeptide, (ii) an agent suitable for keeping pH in the range of from about 4.0 to about 8.0; (iii) an antioxidant; and (iv) an agent selected from the list of: a calcium salt, a magnesium salt, or a mixture thereof.

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29. A method for inhibiting tissue factor mediated reactions in a subject, the method comprising administering to a subject in need thereof an effective amount of an aqueous liquid composition comprising (i) a modified factor VII polypeptide, (ii) an agent suitable for keeping pH in the range of from about 4.0 to about 8.0; (iii) an antioxidant; and (iv) an agent selected from the list of: a calcium salt, a magnesium salt, or a mixture thereof.

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